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LETTERS AND CORRESPONDENCE

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Fig. 1. Skin lesions on neck and legs. Case 1.

Post-Chemotherapy Sweet's Syndrome in Three Patients With AML

To the Editor: Sweet's syndrome (SS), called ''Acute Febrile Dermatitis,'' has been associated with Acute Myeloid Leukemia (AML) [1]. The low frequency of this association (6%) is even rarer with neutropenia [2]. Here we report three cases of AML with SS during the postchemotherapy period.

The skin lesions of SS are soft nodules, usually in the arms, legs, and trunk [3]. The histology shows a perivascular neutrophil infiltrate in the dermis. It is associated with leukocytosis, fever, arthromyalgia, and sometimes ocular and renal symptoms. The physiopathology of SS is still unknown. The use of ATRA, CSFs, and other cytokines has now been related to the appearance of SS. Half of the cases described were idiopathic.

Case 1 was a female, aged 64, with hematomas and malaise, white blood cell count (WBC) 5.9×10^9/L, with 40% blast cells. She was diagnosed with AML-M1 and treated with a 3-7 regime, achieving complete remission. She repeated treatment for consolidation and, on the second day postreatment when granulocytes were 2.9×10^9/L, she developed flu-like symptoms, fever, and painful erythemato-violet confluent dermic lesions in the legs and neck (Fig. 1). The skin biopsy showed a dense perivascular inflammatory infiltrate with frequent signs of leukocytoclasis, necrosis, and intense edema, not affecting the wall vessel.

Case 2 was a female, aged 27, complaining of fever, hematomas, gingivitis, and gingivorragies, WBC 5.6×10^9/L (28% blasts, 13% promyelocytes). Coagulation tests confirmed a DIC picture. Bone marrow (BM) showed massive blastic infiltration, diagnosed with AML-M3. She was treated with a 3-7 regime and ATRA. On the fourth day postreatment when she had granulocytes 0.7×10^9/L, she developed fever, arthralgia, and myalgia, with a cutaneous manifestation similar to the previous case in the face and forehead. The biopsy showed an intense edema in the dermis and a neutrophilic infiltrate among the collagen fibers.

Case 3 was a male, aged 65, with malaise, asthenia, anorexia, and weight loss, WBC 28×10^9/L. Blastic infiltration of AML-M4 cells was 90% in BM and 60% in peripheral blood. He was treated with the 3-7 regime. On the fifth day postchemotherapy, he had arthromyalgia, fever, painful maculopapulomatous red-violet lesions on the skin of the arms and neck, and granulocytes were 0.34×10^9/L. The biopsy shows dermic edema with neutrophilic infiltrate without necrosis.

All three patients had fever and cutaneous lesions unresponsive to antibiotics, which rapidly disappeared with prednisone (1 mg/k/p.o./daily). In the cases reported of SS associated with AML, the SS exists at the time of diagnosis and is the reason for the consultation. This was not seen in any of our three patients [1]. In these cases, lesions appeared between the first and fifth day post-chemotherapy when two of the patients were neutropenic. In patients with AML, SS is usually more serious, but not in our cases. Two of our patients had lesions on the neck, although this localization is rare [3]. Skin lesions are frequent in patients with AML and are often confusing. We believe it is important to remember that they may correspond to SS. By keeping this possibility in mind, correct therapy can be initiated and unnecessary additional treatments can be avoided.

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Successful Thrombolysis for Acute Myocardial Infarction in Type I von Willebrand's Disease (vWD)

To the Editor: Antithrombotic drugs are contraindicated in patients with inherited coagulation disorders, thus making difficult the treatment when they present with acute thrombotic syndromes. Yet, several workers have reported thrombosis in various districts, including coronary arteries, in haemophilia patients, contradicting the notion that congenital clotting deficiencies may have a protective effect on thrombosis [1]. We report the case of a patient with a massive acute anterior myocardial infarction (AMI), who was successfully and uneventfully treated with recombinant tissue plasminogen activator (rtPA).

A 61-year-old man with vWD type I (ristocetin cofactor activity 20%) was admitted to the coronary care unit because of an anterior AMI. He was known to have three-vessel coronary artery disease that had been stable for the last 2 months and was on a waiting list for surgical revascularization. All cardiac surgery theatres were operating and no space would have been available for the next 3 hr. After consultation with the haemathologist on duty, front-loaded rtPA was started, followed by i.v. sodium heparin titrated to aPTT and continued for the following 48 hr. Mild gum bleeding started after 1 hr and continued for a further 6 hr. Epistaxis and haematuria also appeared after 5 hr and while the former was quickly arrested by nose packing, the latter lasted for about 24 hr. Haemoglobin dropped from 14.7 to 8.9 g/dl and haematocrit from 44 to 27% 48 hr after admission, requiring transfusion of 2 U of concentrated red blood cells. Myocardial enzyme release peaked at 10 hr from the beginning of rtPA administration (CK 2838-MB 197 U/L). By the end of thrombolysis the patient became asymptomatic and the ECG evidenced a marked reduction of ST segment elevation, small (<0.2 mV) Q waves, and poor progression of R waves in V2-V4. After pre-treatment with a total of 8,000 U of factor VIII concentrate, on the eighth day of admission the patient underwent successful surgical myocardial revascularization while still receiving factor VIII concentrate, without any major haemorrhagic or thrombotic complication. He was finally discharged well and asymptomatic on day 17, with a haemoglobin level of 12 g/dl and haematocrit 38%.

Most of the previously reported cases of AMI in patients with vWD disease have been observed during factor replacement [2–4]. Once acute thrombosis has occurred in such patients, the use of antithrombotic therapy is usually avoided because of the danger of haemorrhagic complications. To our knowledge, this is the first report of myocardial infarction treated with r-tPA in a patient with vWD. The use of an aggressive thrombolytic strategy resulted in the prompt disappearance of chest pain and ST segment changes, moderate release of cardiac enzymes, and, most importantly, only minimal bleeding complications. This suggests that, at least in patients with mild forms of haemophilic syndromes and acute major thrombotic events, the use of thrombolytic drugs is reasonable and safe.

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Occurrence of a Myocardial Infarction in a 31-Year-Old Woman With Severe Hypercholesterolemia (Type IIA Hyperlipidemia) Three Years After Mantle Irradiation for Stage IIA Hodgkin's Disease

To the Editor: Complications of mantle field radiotherapy for Hodgkin's disease include acute pericarditis, late constrictive pericarditis, coronary artery disease, valvular heart disease, and myocardial fibrosis [1–3]. There has not been an adequate appraisal of the impact of the well-established coronary risk factors (cigarette smoking, diabetes, hypercholesterolemia, and family history of coronary disease) on the risk for developing heart disease following mantle radiotherapy. A 28-year-old woman presented in May 1989, complaining of a right neck lump. She denied fever, chills, sweats, or weight loss. She had no other significant past medical history. There was a slightly tender 3 × 4 cm right supraclavicular lymph node as well as two right axillary lymph nodes. The remainder of her examination was normal. An excisional biopsy of the supraclavicular lymph node revealed Hodgkin's disease, nodular sclerosis type. She was staged as IIA. The serum cholesterol was found to be 519 mg/dl. The patient was referred for extended field radiotherapy in January 1990. The treatment field was extended mantle. The total irradiation exposure was 4,000 cGy. The next recorded lipid profile was in August 1990 at which time the cholesterol was 544 mg/dl, triglycerides 102 mg/dl, HDL-C 46 mg/dl, and LDL-C 478 mg/dl. Dietary interventions were initiated and Lovastatin therapy was begun.

In November 1992, she presented with an episode of left-sided chest pain radiating to the left arm. An electrocardiogram demonstrated T-wave inversions in leads III and aVF and there were elevations of CPK and CPK-MB, in a typical ''rise and fall'' pattern. A diagnosis of myocardial infarction was made.

On the fifth hospital day, the patient underwent cardiac catheterization (Fig. 1). There was diffuse atherosclerosis throughout the coronary tree with sequential 75 and 90% stenoses in the mid-left anterior descending artery and a 90% stenosis in the distal right coronary artery. She underwent successful 2-vessel angioplasty. She did well until April 1993, when rapidly progressive exertional angina developed. Repeat coronary angiography demonstrated re-stenosis of both LAD lesions. She underwent repeat angioplasty to both of these lesions with a successful result. Since that time, she has had stable Class II angina which has been managed medically.

The age-adjusted relative risk of acute myocardial infarction was 2.56 in patients whose treatment included mediastinal irradiation [4]. Hypertension, but not cigarette smoking or diabetes, was identified as a significant risk factor for death from acute myocardial infarction. The existence of hypercholesterolemia as a possible risk factor was not reported independently.

This patient had significant hypercholesterolemia and developed symptomatic coronary artery disease less than 3 years after the completion of radiotherapy for Hodgkin's disease. Her coronary artery disease developed

Fig. 1. Right coronary artery showing 90% stenosis in the mid vessel, with diffuse disease throughout.

at an age much earlier than is typical for women with her lipid disorder, and earlier than average for patients who develop myocardial infarction following mantle radiotherapy [5]. This suggests that hypercholesterolemia significantly contributed to the development of her coronary disease. The potential to develop accelerated coronary artery disease after radiotherapy for Hodgkin's disease in patients with pre-existing coronary risk factors suggests the need to consider alternative therapy, such as systemic chemotherapy for patients regardless of their disease stage.

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Further Note for the Discrimination of Hb C

To the Editor: Hb C results from a single base substitution at codon 6 of beta globin gene. It migrates like Hb A_2, Hb E, Hb E Saskatoon, and Hb O Arab on alkaline electrophoresis. There are several identification methods at the molecular level [1,2].

Recently, we reported a restriction enzyme digestion protocol for the direct detection of Hb C (β6(A3)Glu→Lys) by Bse RI analysis (GAGGAGN10) discriminating Hb E(β26(GH4)Glu→Lys)), Hb E Saskatoon(β22(GH4)Glu→Lys)), and Hb O Arab (β121(GH4)Glu→Lys) from each other [2].

Hb C is a widespread abnormal hemoglobin in different populations. There are very rare variants of hemoglobin with more than one amino acid substitution in the beta chain migrating about as Hb A_2 on alkaline electrophoresis. There variants are Hb C-Harlem [β6(A3)Glu→Val and β73 (E17)Asp→Asn]; Hb C-Ziguinchor [β6(A3)Glu→Val and β58(E2)Pro→ Arg]; Hb S-Oman[β6(A3)Glu→Val and β121(GH4)Glu→Lys)]. All these variants are reported mainly in individuals of African origin [3].

On a theoretical basis, all these variants abolish the restriction site of BseRI. So further discrimination is needed. All these three variants can be discriminated by Dde I enzyme with the method previously reported for HbS (β6(A3)Glu→Val) [4]. As Hb C does not abolish the Dde l restriction site by dual restriction analysis, verification of Hb C is performed. Hb S-Oman can further be identified by Dde I and dual restriction enzyme analysis with previously reported techniques for β121 variants [5,6].

Whenever a diagnosis of HbC is performed by BseRI restriction enzyme protocol, further analysis of these very rare variants is necessary.

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Pregnancy and Thrombocythemia

To the Editor: I read with interest the article by Pagliaro and colleagues regarding their experience with the outcome of 15 pregnancies in 9 patients with essential thrombocythemia (ET) [1]. We recently published the largest experience from a single institution involving 34 pregnancies in 18 women with ET [2]. Our cases were identified by reviewing all clinical events of 73 women (age < 50 years) with ET seen at our institution during a 16-year period. Patients and their physicians were contacted in each case and a careful and complete obstetric history was obtained. This was done to avoid patient or event selection bias, because uneventful outcomes as well as early spontaneous abortions (SA) may be underreported. It would be useful to know how the patients were selected and the events were recognized in the study by Pagliaro et al. [1].

Both studies [1,2] report an increased rate of nonelective fetal loss. In our study, this was due primarily to first-trimester SA. Similar to our observation, a recent review of the literature discloses an overall miscarriage rate of 43%, a first-trimester SA rate of 36%, and an intrauterine death (IUD) rate of 5% [3]. The SA rate of 13% in the Pagliaro et al. study was unusually low and the IUD rate of 20% unusually high. Nevertheless, the clinically relevant question is whether specific therapy influences outcome. In our study, the use of acetylsalicylic acid (ASA) did not affect the frequency of SA. It is implied in the Pagliaro et al. study [1] that the use of ASA in association with heparin may result in a better outcome. It should be noted, however, that heparin treatment of their patients was started during the second trimester and that the clinical course during the last two trimesters in pregnant women with ET is usually uneventful, even without any form of therapy [2,3].

Therefore, we do not recommend any form of therapy in ''low-risk for thrombosis'' patients with ET who are or may become pregnant [4]. A previous history of SA may be the best and only predictor of a similar subsequent event [2], and in such patients, a systematic study in the therapeutic use of ASA or a platelet-lowering agent may be considered. Specific therapy with a platelet-lowering agent is recommended for those patients with a previous history of thrombosis [4,5]. Hydroxyurea, interferon alfa, and anagrelide are the platelet-lowering agents usually considered in ET [4]. Because of the concern about teratogenicity, the use of hydroxyurea is discouraged during the first trimester. Currently, anagrelide is not advised for use during pregnancy. Because interferon alfa lacks mutagenicity, does not cross the placenta, and has been used successfully in pregnant women with ET, it may be the best possible option given the limited data [3].

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Arterial and Venous Thrombosis Associated to Combined Deficiency of Protein C and Antithrombin III

To the Editor: Congenital deficiency of natural anticoagulants causes recurrent thromboembolism [1], however, combined deficiency of these proteins has rarely been described [2–5]. We report a 52-year-old male with a thrombosis of the right humeral artery at age 40 years; as a consequence he lost the limb. He was evaluated for thrombophilia the first time in 1983 because of an arterial occlusion of the right popliteal artery requiring amputation. His medical history was also significant for a right hydrocele, mild venous insufficiency of the left leg, and chronic obstructive pulmonary disease. Antiplatelet agents were initiated and before the etiology of his thrombophilia was established, he was lost to follow-up until 1990 when returned because of a pneumonia and an acute venous syndrome of the left leg characterized by swelling, warmth, and erythema. Venography and Doppler ultrasound showed complete obstruction of the femoropopliteal system and other findings suggesting chronic thromboembolism. Once discharged, he was lost again to follow-up without a diagnosis. He returned in 1994 because of sudden pain, coldness, and numbness of the anterior half of the left foot without previous intermittent claudication. Before starting heparin (20 UI/kg/h), plasma samples were obtained. The results of antithrombin III (AT-III), protein C (PC), as well as other hemostatic parameters are shown in Table I. Despite receiving heparin up to 60 UI/kg/h, no therapeutic effect on the partial thromboplastin time test (PTT) was achieved. Twelve hours later his condition worsened and he had absence of pedal, tibial, and popliteal pulses, cyanosis, decreased skin temperature, and gangrene up to the knee. The arteriography demonstrated total occlusion of the superficial femoral artery and the left leg was amputated. Anatomopathological studies showed recent and complete obstruction of the artery. Evolution post-surgery was unremarkable and no source of emboli was found in the heart or aorta. Three weeks after surgery, AT-III and PC assays were repeated showing the same deficiency pattern and heparin and antiplatelet agents were restarted. Again, despite this therapy PTT remained within normal limits. Four weeks after surgery, he suddenly developed dyspnea and chest pain with abnormal arterial gases. A pulmonary thromboembolism was diagnosed and he died 48 h later because of multi-organ failure.

TABLE I. Hemostatic Features in a Combined PC and AT-III Deficiency*

Assay	Before heparin	After last amputation
Functional test		
PC	52%	40%
AT-III	38%	30%
AT-III heparin cofactor	28″	28″
Protein S (free)	102%	110%
Plasminogen	97%	
C1-inhibitor	95%	
Immunological tests		
PC	46%	40%
AT-III	0.09 mg/ml	0.07 mg/ml
tPA	10 ng/ml	
Coagulometric tests		
Factor II	88%	92%
Factor X	110%	99%
Prothrombin time	13.1″	13.2″

*Normal values: Functional PC: 75–129%; functional AT-III: 75–120%; AT-III heparin cofactor: >100″ in the presence of heparin; antigenic PC: 80–120%; antigenic AT-III: 0.22–0.39 mg/ml.

This patient had a combined deficiency of AT-III and PC. Few cases with this association have been reported [2–4]. Unfortunately, no relatives were studied. He suffered multiple venous and arterial thromboses, although the latter are infrequent complications in PC or AT-III deficient patients. Cases reported with multiple deficiencies of natural anticoagulants [2–5] have been primarily young patients without arterial thrombotic events. In this case, there may have been a contributory effect of the secondary polycythemia with its subsequent increase in the blood viscosity. However, it seems that the deficiency of the two most important natural anticoagulants had a main role in his prothrombotic state. This case strongly suggests that the risk of arterial and venous thrombosis increases

in patients with multiple deficiencies of natural anticoagulants as other age-related thrombotic risk actors appear in the patient.

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Haemostatic Abnormalities in Dengue Haemorrhagic Fever in the New Delhi Outbreak, India

To the Editor: The recent epidemic of dengue haemorrhagic fever (DHF) in New Delhi, India (from August–November 1996) enabled us to gain an insight into some of the mechanisms responsible for bleeding in DHF.

One hundred and twenty-seven patients (122 adults, median age 25 years) were diagnosed to have dengue haemorrhagic fever by the WHO criteria [1,2]. There was a male preponderence (male:female = 87:40). Haemorrhagic manifestations were present in all patients at admission or they appeared within the first 3 days of the illness. Platelet counts performed approximately 4.5 days after hospitalisation revealed normalisation of the initial thrombocytopenia in 71 patients. Thrombocytopenia persisted to be severe in 12 (21.4%), moderate in 36 (64.28%), and mild in 8 (14.28%) cases. There was no correlation between the platelet count and clinical bleeding. In 4 cases with severe persistent thrombocytopenia, bone marrow aspirates at 7 to 10 days of illness revealed reactive bone marrow with an adequate number of megakaryocytes as has been reported by Bierman et al. At 4 days, however, they had found the bone marrow to be hypocellular [3].

Platelet aggregation was studied in 6 patients who were bleeding but had reached platelet counts of more than 90,000 (90–156 × 10^3)/cu. mm. With ADP, the degree of aggregation was reduced in 5 (17.5 ± 10%) and with Adrenalin in 4 (11 ± 9%) cases, respectively. In contrast, earlier studies have shown normal platelet aggregation with collagen, ADP, and adrenalin [3]. Immunofluorescent studies to detect anti-platelet antibodies were performed in 3 patients (platelet count between 40–60 × 10^3/cu mm). Their presence (+++) was demonstrated in all of them, suggesting an immune-mediated etiology for thrombocytopenia. This, along with associated platelet dysfunction in some cases, may contribute to the observed absence of correlation between the platelet count and bleeding in DHF. Platelet transfusions did not affect the ultimate outcome of patients. Their role in the management of bleeding in these patients, therefore, remains controversial.

Coagulation studies in 76 patients revealed thrombocytopenia with mild prolongation of activated partial thromboplastin time (APTT) to be the commonest abnormality, seen in 29/76 (38.15%) cases (Table I). The APTT values ranged between 48 and 62 sec. In 5 such patients with APTT of 54, 50, 50, 52, and 56 sec, respectively, on whom factor VIII: C was assayed, it was reduced to 33–42% of normal pooled plasma. Screening for FVIII inhibitors performed in 3 of these 5 patients was negative. Prolonged APTT in these cases may have been due to reduced F VIII:C levels consequent upon mild consumptive coagulopathy or secondary to endothelial damage adversely affecting the F VIII synthesis.

In 10 cases (13.15%), both APTT and PT were prolonged with a normal thrombin time (TT). The APTT values ranged between 48–65 sec and PT values between 14.5–18 sec. Fibrinogen degradation products (FDP) tested in 3 such patients were mildly elevated (between 10 and 40 μg/ml). Although this may have been secondary to liver derangement, possibility of a mild consumptive coagulopathy cannot be excluded. An earlier study has also demonstrated existence of an underlying mild consumptive coagulopathy in DHF without any patient showing acute DIC [4]. We, however, observed marked prolongations of PT, APTT, and TT, thrombocytopenia and microangiopathic anaemia suggesting acute DIC in 4 (5.2%) cases, all of whom expired on account of dengue septicemic shock syndrome. The remaining 72 patients, managed by intravenous fluid infusions, survived.

TABLE I. Haemostatic Abnormalities in Dengue Haemorrhagic Fever*

S. no.	Abnormality	No of patients (%)	FDP	FVIII levels	FVIII inhibitor	Outcome	Probable cause
1.	Isolated thrombocytopenia	14 (18.9%)	ND	ND	ND	S	Viral injury Ab mediated liver damage
2.	↑ APTT, N PPT, ↓ PC	29 (38.15%)	ND	5/5 (33–42%)	Negative 3/3	S	?Consumptive coagulopathy
3.	↑ APTT, ↑ PPT, N TT, ↓ PC	10 (13.15%)	3/3 (10–40 μg/ml)	ND	ND	S	? Consumptive coagulopathy ? Liver derangement
4.	↑ PPT, ↑ APTT, ↑ TT, ↓ PC	4 (5%)	ND[a]	ND	ND	Expired	Acute DIC
5.	Normal coagulation tests and PC	19 (25%)	ND	ND	ND	S	NA
	Total	76					

*S: survived; PC: platelet count; N: normal; Ab: antibody; ND: not done; NA: not applicable.
[a]Peripheral smear showed microangiopathic hemolytic anemia.

The current studies highlight some of the unusual features encountered in the New Delhi Dengue outbreak. One hundred and twenty-two of 127 were adults (>14 years) as against the reported high frequency in children. That the platelet transfusions should not have helped is also unusual. While immune mediated platelet destruction may be a possible mechanism underlying thrombocytopenia in DHF, this needs elucidation in a larger group of patients by antiplatelet antibody demonstration and platelet survival studies [5]. The mechanisms underlying isolated prologation of APTT as well as other coagulation abnormalities also need to be studied further, since these may be important additional factors contributing to haemorrhage.

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Use of Erythropoietin (EPO) in Peripheral Stem Cell Transplantation

To the Editor: Estrin et al.'s recent letter describing the use of Erythropoietin (EPO) in peripheral stem cell transplantation is an advance in the management of Jehovah's Witnesses who cannot accept blood products [1]. From our experience as primary care physicians and haematologists working closely with this community, we highlight two issues that may preclude the widespread acceptance of this strategy.

First, recombinant EPO is often stabilized in human serum albumin (HSA), a component of blood. Freeze-dried EPO (Boehringer Mannheim, Indianapolis, IN) is preferable to some patients because it does not contain human or animal blood products. This may not be a major area of contention as members of Jehovah's Witnesses Hospital Liaison Committees distribute publications to their medical consultants on the use of erythropoietin in accelerating post-surgical haematocrit recovery [2].

A more serious issue relates to the use of ''shed'' blood, which is not at all times in continuity with the circulation and as a matter of conscience may be unacceptable to some patients. Pre-deposit autologous blood programs to permit major orthopaedic and vascular surgery have not been accepted by this community and peripheral blood stem cell collections could similarly be rejected as they contain normal peripheral blood elements.

Haematologists caring for Jehovah's Witnesses should be aware of these issues and the need to discuss them fully.

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Sézary Syndrome in an HTLV-I-Seronegative, Genome-Positive Japanese

To the Editor: Human T-cell lymphotropic virus type I (HTLV-I) is the causative agent of adult T-cell leukemia (ATL) and tropical spastic paraparesis/HTLV-I-associated myelopathy. The vast majority of patients with these diseases as well as asymptomatic HTLV-I carriers have antibodies to HTLV-I. Whether mycosis fungoides and Sézary syndrome are associated with HTLV-I infection remains controversial. Some investigators found HTLV-I sequences in these conditions, whereas others failed to confirm this observation [1]. Here we report a seronegative HTLV-I carrier who developed Sézary syndrome not associated with HTLV-I.

The patient was a 58-year-old man who was admitted with generalized erythroderma in May 1990. Lymph nodes, up to 1.5 cm in diameter, were palpable in the axillary and inguinal regions. The leukocyte count was 12,700/μl with 20% abnormal lymphoid cells having cerebriform nuclei. Peripheral blood mononuclear cells (PBMC) contained 86.9% CD4 cells and 5.9% CD8 cells. Serological studies were consistently negative for HTLV-I by particle agglutination (Fujirebio, Tokyo), ELISA (Eisai, Tokyo), indirect immunofluorescence, and Western blot (Eisai). Antibody to HTLV-I $p40^{tax}$ was also negative by ELISA. A skin biopsy specimen showed Pautrier's microabscesses and perivascular infiltration of abnormal

TABLE I. Primers and Probes Used for PCR Analysis

Region amplified	Primer (probe) designation	Primer (probe) position	Product size (bp)
		1,301–1,320	
gag		1,420–1,401	120
		(1,359–1,378)	
	SK54	3,365–3,384	
pol	SK55	3,483–3,465	119
	(SK56)	(3,426–3,460)	
	E30	5,627–5,648	
env	E34	5,792–5,771	166
	(E33)	(5,713–5,735)	
		7,341–7,360	
pX		7,460–7,441	120
		(7,364–7,383)	
		23–42	
LTR		426–407	404
		(331–351)	

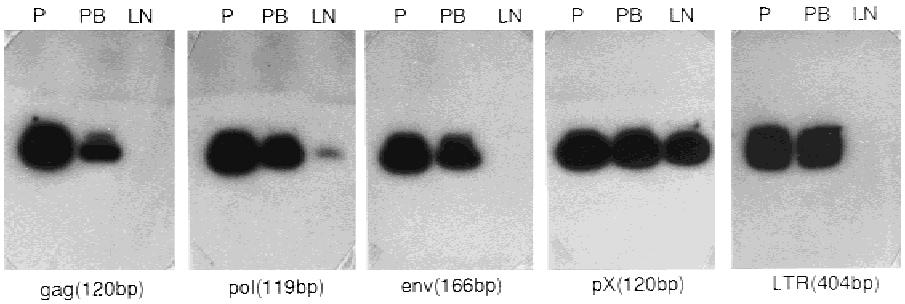

Fig. 1. PCR analysis, showing *gag*, *pol*, *env*, *pX*, and LTR sequences in DNA from peripheral blood (PB) and *pol* and *pX* sequences in DNA from lymph node (LN). P is a positive control.

lymphoid cells in the upper and mid dermis. A biopsied inguinal lymph node was also infiltrated by abnormal lymphoid cells. We performed polymerase chain reaction (PCR) analysis using five sets of primers and probes specific for HTLV-I *gag*, *pol*, *env*, *pX*, and LTR regions (Table I). PBMC DNA was positive for all five sequences, while lymph node DNA was positive for *pol* and *pX* sequences only (Fig. 1). However, Southern blot hybridization revealed no evidence of HTLV-I integration in PBMC DNA after digestion with *Eco*RI or *Pst*I. Furthermore, no monoclonal integration of HTLV-I was found in PBMC DNA by inverse PCR, which is highly sensitive in detecting monoclonal integration of HTLV-I [2].

Thus, our patient was considered to be a seronegative HTLV-I carrier who developed HTLV-I genome-negative Sézary syndrome. Kikuchi et al. [3] also reported two seropositive patients with cutaneous T-cell lymphoma in which no monoclonal integration of HTLV-I was detected by Southern blot hybridization and inverse PCR despite PCR positivity for three or all of the *gag*, *pol*, *env*, and *pX* sequences.

Previously, we described a seronegative patient with ATL whose leukemic cells harbored the full genome of HTLV-I [4]. The prevalence of seronegative carriers of HTLV-I is poorly understood. In a survey in Okinawa where HTLV-I is endemic, Miyata et al. [5] found 17 HTLV-I carriers among 1,015 high school students and one of them was a seronegative carrier. To resolve the controversy regarding the association of HTLV-I with mycosis fungoides and Sézary syndrome, patients should be evaluated first for HTLV-I infection by serology and PCR, and then for monoclonal integration of HTLV-I by Southern blot hybridization and/or inverse PCR. PCR positivity alone with or without seropositivity is consistent with polyclonal integration of complete or defective HTLV-I and makes its causal role less likely in the pathogenesis of these diseases.

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